Standard Operating Procedure Title: Site Quality Management Plan Development	NIH/NIAID/DMID/OCRA OP.QM001 New Issue
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I.   Purpose:

To describe the requirements and procedures for Division of Microbiology and Infectious Diseases (DMID) -sponsored research sites in the creation and implementation of a site-specific quality management plan (QMP).

II.   Applies to:

All sites conducting research under the sponsorship of the DMID.

III.   Responsibilities:

Principal Investigator (PI) or designee: Responsible for the development and implementation of the QMP.

Office of Clinical Research (OCRA) Quality Assurance (QA) Coordinator or designee: Reviews the draft QMP and accepts the final QMP.

IV.   Procedures:

See Appendix A - Flow Diagram
See Appendix B - Glossary of Terms.

A. Site-Specific Plan:

1. The Principal Investigator or designee drafts the site-specific QMP, using the DMID-approved template as the preferred option. (See Appendix C.) Other format may be used as long as the DMID elements are all present.

2. Site submits dated, version-controlled draft QMP to DMID QA Coordinator for review. This includes tools to be used in implementation of the plan.

3. DMID reviews the plan to ascertain if required elements are present and the plan meets requirements. This responsibility may be delegated to CTM QM group.

4. If modifications are needed, DMID and/or CTM QM group work directly with the site to amend the document.

5. Once the plan is deemed to be acceptable, DMID or CTM QM group sends an acceptance notice to the site.

6. The site files the acceptance notice in the Quality Management (QM) binder or file. The QM file or binder is used maintain the QM plan and completed tools and reports. It is kept separate from the study/trial files.

B. Quality Management Plan (QMP) Implementation:

Quality management is an ongoing process. At periodic intervals, the findings from the review (audit) of site regulatory files and research charts (subject records) are to be aggregated and analyzed to look for trends and identify opportunities for improvement.

Audits of site regulatory files should be conducted annually at a minimum. Review of subject records is an ongoing process

1. All Quality Assurance (QA) or Quality Control (QC) audits should be documented on site-specific tools. (See Appendix D, Chart Audit Tool, Appendix E, Regulatory File Review Tool, and Appendix F, Quality Management Summary Report, for examples.)

2. When reviewing subject records, the following indicators (key components) should be reviewed as applicable:

    o   Consent and assent forms
    o   Eligibility
    o   Concomitant medications
    o   Test article administration
    o   AE/SAE reporting
    o   Study endpoints
    o   Missed visits and follow up
    o   Signatures as required
    o   Treatment/study discontinuation
    o   Reactogenicity (for vaccine studies)
    o   Other Study-specific indicators

3. When reviewing regulatory files, documents as listed in the International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (GCP) E6, Section 8, Essential Documents for the Conduct of a Clinical Trial, should be included, as well as any study-specific or sponsor-required document.

4. Periodic (e.g., monthly or quarterly) reports should be prepared which summarize findings of QA and QC reviews. These reports should be shared with the PI and site staff, noting areas for improvement as well as improvement noted from previous summary reports.

C. Evaluation of the QM Plan;

The site staff, including the PI, should review the plan at least annually for effectiveness, e.g. "Does the plan meeting the needs of the site? Is the plan identifying opportunities for improvement? Is there a need to add or modify existing indicators?" If the plan is modified to increase effectiveness, the submission process is reactivated following the steps in Section A, Site-Specific Plan.

V.   Appendices

Appendix A – Flow Diagram
Appendix B – Glossary of Terms
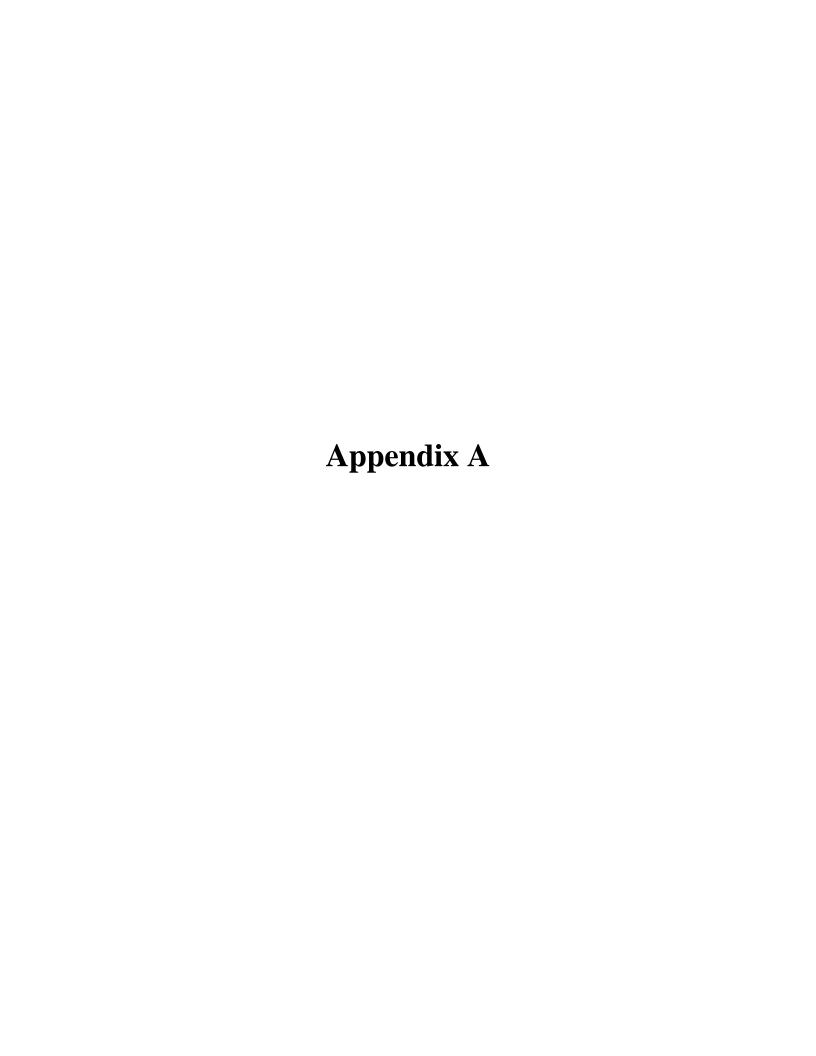Appendix C – Quality Management Template
Appendix D – Chart Audit Tool
Appendix E – Regulatory File Review Tool
Appendix F – Quality Management Summary Report

VI.   Documents Referenced

International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (GCP) E6, Section 8, Essential Documents for the Conduct of a Clinical Trial

Appendix A

Site-Specific Quality Management Plan (QMP)

Site-Specific Plan Development

Principal Investigator (PI) drafts and submits dated,
version controlled QMP to DMID for review

DMID reviews the QMP to determine if all elements in the template are present

DMID sends a notice of acceptance to the sites once all elements are present
The notice is to be filed at the site with the QMP and other QM documentation

QMP Implementation

Site identifies study-specific key components for subject record review

Site identifies study-specific regulatory records for
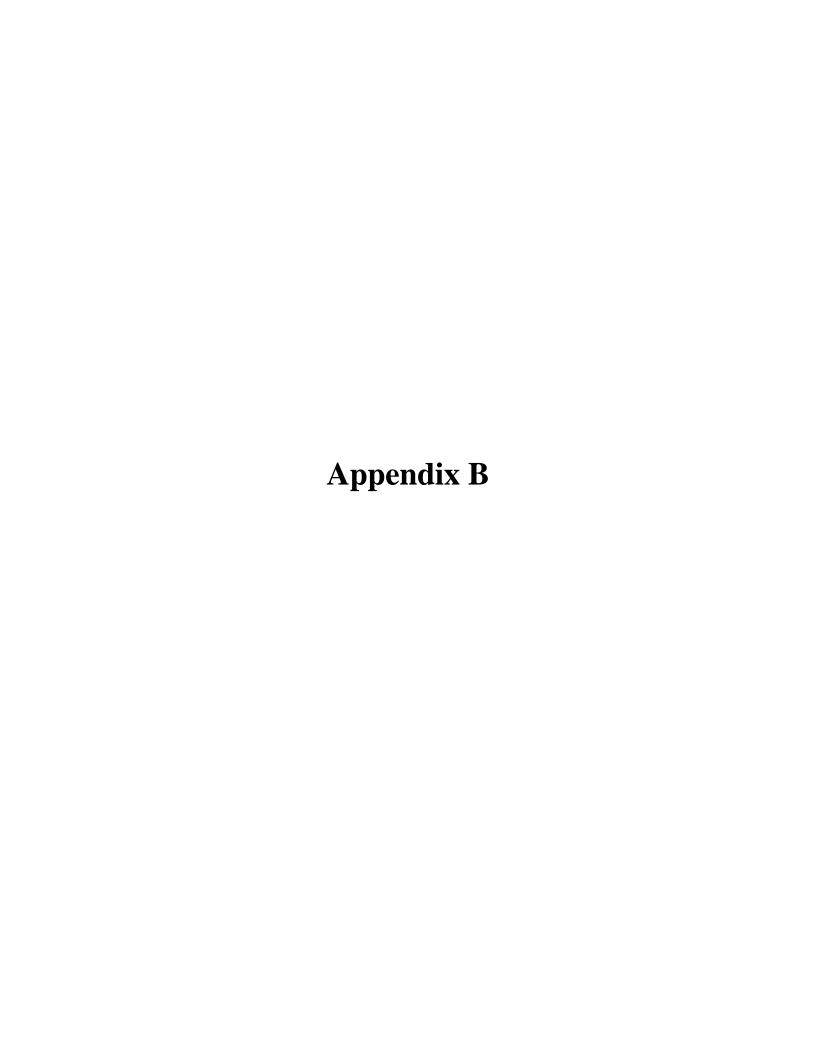review based on ICH GCP E6, Section 8

Findings of the reviews are recorded on site-specific tools

Audit findings should be periodically summarized and shared with the
PI and site staff noting both areas for improvement
and improvement from previous summary reports

Evaluation of the QMP

The QMP should be reviewed at least annually to determine if revisions are needed

If revisions are made, the submission process is reactivated

Appendix B

APPENDIX B: GLOSSARY OF TERMS

- **Quality Management**:

  Quality Management is the term used to describe the overall process of assessing the quality of processes within a system, with the goal of quality improvement. The term quality management encompasses both quality control (QC), and quality assurance (QA). Other terms often used are CQI (Continuous Quality Improvement) or TQM (Total Quality Management)

- **Quality Assurance:**

  Quality Assurance (QA) is a comprehensive, proactive process of the review (audit) of all components of research records to assess adherence to policies and regulations and evaluate the accuracy of the records (e.g., comparison of source documents to case report forms and the protocol, or review of regulatory documents against sponsor/study requirements and the regulatory requirements). This process is typically sample-based and retrospective with the aim of identifying any trends that may require corrective action.
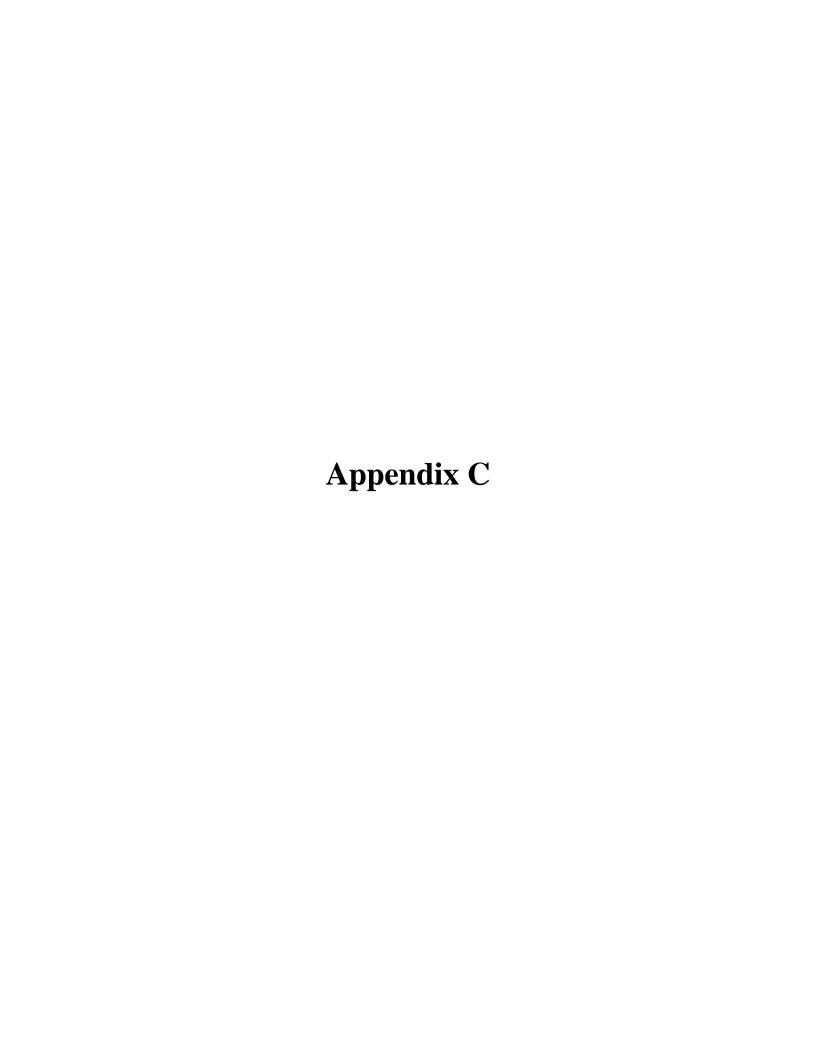
- **Quality Control:**

  Quality Control (QC) is the ongoing process of checking completed forms for completion and logic. It is a review (e.g., daily review of case report forms), and is concurrent, as opposed to retrospective.

- **Quality Management Plan:**

  A quality management plan is a formal, written document that details the responsibility, scope, and frequency of activities in place that are designed to assess the effectiveness of the conduct of clinical trials at the site level.

- **Quality Audit:**

  An evaluative process for determining the compliance and/or effectiveness of a process or a system. A quality audit is a positive and constructive process. It helps prevent problems in the organization being audited by identifying the activities apt to create problems.

Appendix C

DMID Quality Management Plan

Site Name, Location	Site Number (If Applicable)
Principal Investigator Responsible for QM Program	Person Responsible for day-to-day implementation of QM activities
Person Responsible for QA Audits of records (retrospective sampling)	Person responsible for QC (100%) review of case report forms (must not be person who completed the CRF)

Describe the process and frequency of QA audits of the research records, including the sample size to be audited (e.g. 10%), and how records for review will be prioritized (e.g. new protocols, complex protocols). This process must be conducted by a clinical person, and should not be the person who originally completed the CRF and source documentation.

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Describe the process, frequency, and documentation of audits of regulatory files. Attach audit tools to be utilized. :

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Describe the process, frequency, and documentation of preparation of summary reports of quality management activities, and how these will be prepared. These reports should include aggregated information from clinical chart reviews, quality control checks, and regulatory file reviews at a minimum:

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_____
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Listed are the key indicators to be measured for QA audits:
(Additional indicators may be added at site discretion)

Indicator	Additional Indicators
Informed Consent	
Eligibility	
Concomitant Medications	
Test Article Administration	
AE/SAE reporting	
Endpoint reporting	
Missed visits and follow up	
Treatment/study discontinuation	
Signatures as required	
Reactogenicity (for vaccine studies)	

Note: QA reviews are to include comparison of CRF to Source documents and protocol for agreement and accuracy. For studies which include electronic data capture (EDC), the source documents must be compared to the database for data fields entered into the electronic system.

Describe the process for the conduct of QC of CRFs for logic, completion, and accuracy. Include the frequency, and how the QC process will be documented (e.g. checklist, log sheet). If there are quality control or query reports from the data management center, include a description of how these tools will be utilized for corrective action:

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If this is a main unit with subunits, describe the process for staff from the main unit to visit the subunit(s) to audit records, including the frequency and sample size to be audited:

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Identify and attach the audit tools to be used for QA reviews. Documentation of QA should include the protocol reviewed, subject/record identification #, scope of review, date of QA audit, timeframe covered in the audit, reviewer's name, and problems identified/resolved.

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Describe the mechanism for recording/reporting summary audit findings. How will the report be shared with PI and staff? How will this be documented? How often will it occur?

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Describe the plan to address adverse trends that are identified through the internal QM process (both QA and QC) Include a description of corrective action plans which may be implemented.

_____
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_____
Signature of person preparing QM Plan (print name next to signature)

Date of this Plan:_____

Appendix D

CHART AUDIT FOR PROTOCOL#_____

PID#_____ Reviewed from WK/Visit_____Through WK/Visit_____ Date of Review_____

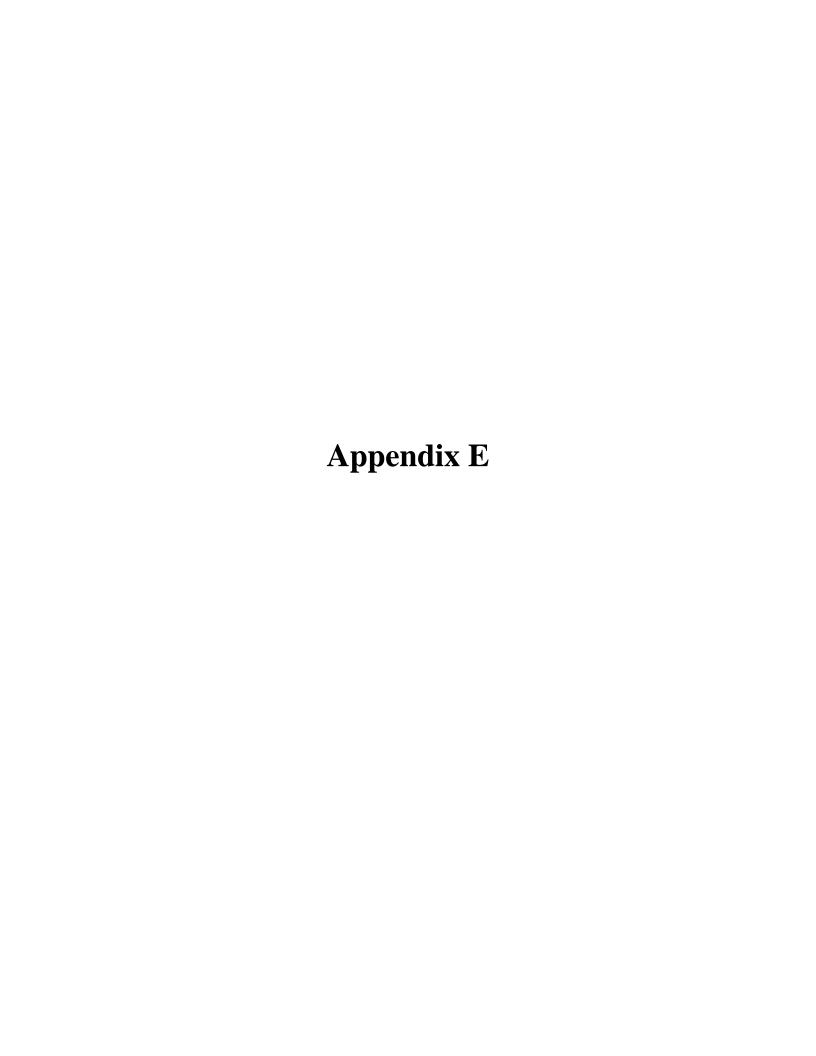| Indicator	Criteria	YES	NO	N/A	Comments
Consent	Current, approved version of consent signed?				
	Participant signed and dated (in ink) consent, prior to study-specific procedures?				
Eligibility	All inclusion criteria met and documented?				
	Participant meets none of the exclusion criteria, and documented?				
Concomitant meds	Source documentation and CRF consistent?				
	Is participant taking any prohibited meds?				
Test Article dosing	Has test article been administered per protocol and documented accordingly?				
	For vaccines: reactogenicity recorded at appropriate timeframes with appropriate follow-up?				
AE/SAE Reporting	Adverse events recorded and reported properly?				
	Are there any missed (unreported) AEs?				
	Are there any missed (unreported SAEs?				
Endpoints	Has the participant reached any protocol-defined endpoints?				
	If yes, are they documented properly and protocol followed?				
Missed Visits	Has the participant missed any visits?				
	If yes, are they documented, with attempts to contact participant noted?				
Signatures, etc.	Are all entries signed and dated?				

	Are signatures of personnel signing present in the staff signature list in the regulator binder?				
	Are all error corrections properly executed?				
Treatment/study discontinuation	If the participant has discontinued treatment or study, have all protocol-required steps been followed?				
Miscellaneous	Any protocol-specific problems/omissions noted?				
	Are DMID Source Documentation Guidelines being followed?				
	Have all protocol-required lab tests and procedures been performed?				
	If CRFs are used as source docs, are they signed and dated?				

Note: Source documentation to be compared to CRF and protocol for agreement. For electronic data capture (EDC), source documentation is to be compared to database for agreement. Be sure to include lab reports, diagnostic reports, etc., in review. Complete this tool for each participant record being reviewed. Problems/errors noted should be resolved, with corrections/date/ responsible person being noted in the section below. When completed and all follow up is done, this tool should be filed in the QA binder at the site.

Comment on any "NO" entries in the spaces below:

Problem/error (Refer to "comments" in above section)	Week/Mo/Date	Corrected by/date

Person Performing QA Review:_____

Appendix E

Regulatory File Review Tool

Instructions: List the protocol number, the date range that is being reviewed and the date of the review. Once the review begins, check √the appropriate boxes for each question listed in the criteria section. When the review is completed for all applicable documents, the QA reviewer will sign and date the form. Use the comments section for clarification and action on any "no" entries checked. Regulatory files should be reviewed no less than annually for each protocol.
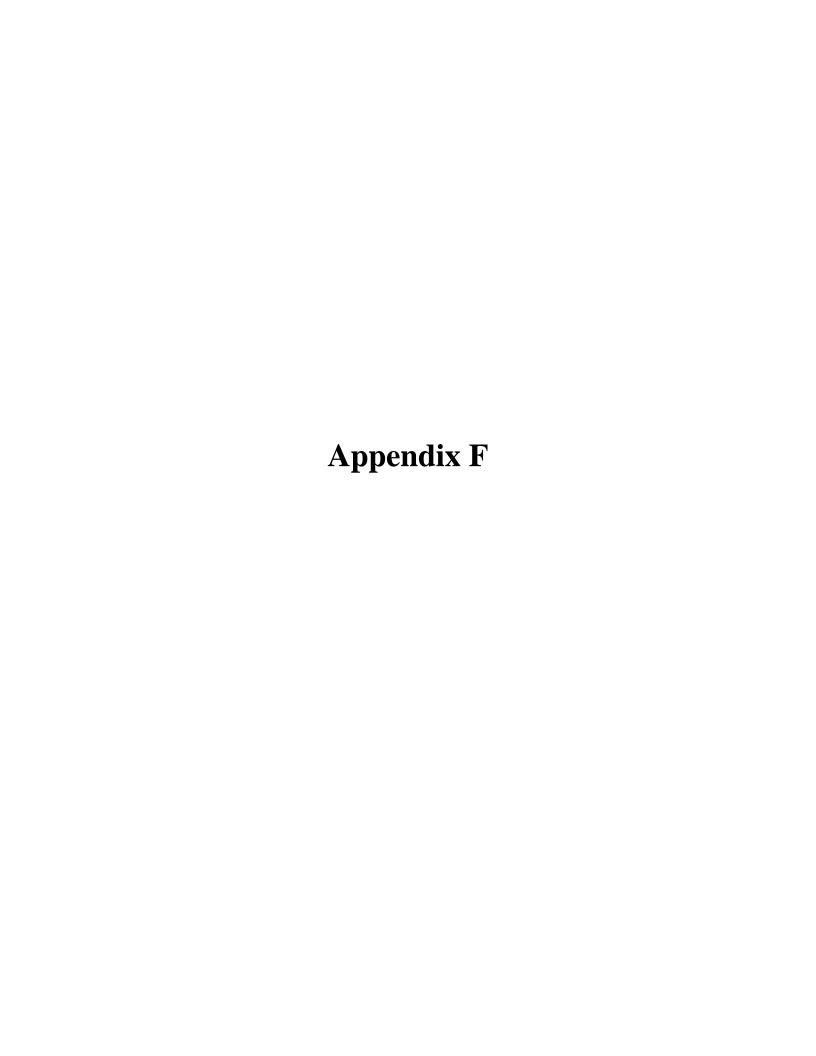
Protocol #_____Reviewed from_____Through_____

Document	Criteria	Yes	No	N/A	Comments
IRB/EC approval	Initial IRB/EC approval for protocol & consent present?				
	Continuing review approval(s) present, annually?				
	Information given to trial subjects approved by IRB and on file? (including advertisements, recruitment scripts)				
	Approvals for any protocol amendments present?				
IRB/IEC membership	Is the IRB roster or membership composition on file? Has it been updated annually?				
Foreign regulatory approvals	If this is a non-U.S. site, is there documentation of foreign regulatory body approval or clearance on file?				
Assurances	Is there a current assurance document from OHRP present?				
Safety Reports	Are safety reports/memos for this protocol on file?				
	Have these safety reports been submitted to IRB/IEC?				
Protocol and Consent	Is a current copy of the protocol and consent on file?				
	Are all previous versions on file?				
Document	**Criteria**	**Yes**	**No**	**N/A**	**Comments**
Sample CRF	Is there a copy of the CRF(s) on file?				

1572/IOR agreement	Is there a 1572 (for IND studies), or an Investigator of Record Agreement on file?				
	Is the document current and accurate?				
CVs	Are CVs present for all key personnel? Are they current?				
Financial Disclosure	Are financial disclosure forms for all key personnel present?				
Investigator Brochures	Are Investigator Brochures present for investigational products?				
	Are package inserts available for approved drugs?				
Laboratory	Are laboratory certifications present for U.S. labs? If not a U.S. lab, are there other certificates of qualification for the lab on file?				
	Are normal ranges for all protocol-required tests on file?				
Investigational product	Is there a sample of label attached to investigational product containers on file?				
	Are instructions for handling of investigational product on file?				
	Are shipping records for investigational product on file?				
	Are decoding procedures for blinded product on file?				
	Is there a master randomization or enrollment list on file?				
Monitoring reports	Are copies of site monitoring reports on file? (Initiation, interim monitoring)				
Signature Key	Is the signature key present for all individuals authorized to make entries in study records?				

Comments/Corrective action to follow up on any "no" entries :

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Reviewer_____

Appendix F

Quality Management Summary Report

Site:_____

Date of Report_____

Person Preparing Report_____

Reporting Period_____

A. <u>Summary of QA/QC Activities for the Reporting Period:</u>
Note: Enter aggregate numbers from completed tools.

QA Activities:

1.   Number of Participant Records Reviewed (List by protocol number):

2.   Protocols Reviewed (List by number):

3.   Number of Regulatory Files Reviewed (List by protocol number):

B. <u>Problems/Trends Identified:_____</u>

Protocol #	Problems Identified

C. Corrective Action Implemented:_(*Note planned date of completion*)

Protocol #	<u>Corrective Action and planned date of completion</u>

D._Improvement Noted (effectiveness of corrective action implemented)_____

Protocol #	Improvement and date

E. **QC problems/ trends identified through site QC checks or data management center reports or queries (note issues identified and corrective action implemented):**

Protocol #	Trends identified & Corrective Action Implemented:

F.Plans for next Reporting Period:_____

QA Coordinator (signature and date)_____

Reviewed by Principal Investigator (signature and date)_____

Note: This report is to be utilized for the summary of QA/QC activities, and includes the aggregated information from completed chart review tools, regulatory file review tools, and other site-developed tools such as QC checklists. This report and any other QA/QC report tools should be filed in a separate quality management binder, separate from site regulatory documents.